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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/468,610	06/06/95	BURTON S	[illegible]

18M2/0313

GENENCOR INTERNATILNAL INC.
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EXAMINER	
WEBER, J	

ART UNIT	PAPER NUMBER
1808	

DATE MAILED: 03/13/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
08/486,610	Burton et al.
Examiner	**Group Art Unit**
Jon P. Weber, Ph.D.	1808

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☐ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due two months from the date of the Notice of Appeal filed on *24 Feb 1997* (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *24 Feb 1997* has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

☒ The proposed amendment(s):

☒ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☐ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☒ Applicant's response has overcome the following rejection(s):
112, first paragraph

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
see attachment

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: _____

Claims objected to: _____

Claims rejected: *1-5 and 7-23*

☐ The proposed drawing correction filed on _____ ☐ has ☐ has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ .

☐ Other

Claims 1-5 and 7-23 have been presented for examination.

The response with after FINAL amendments filed 24 February 1997 has been received and will entered in part with the appeal brief. The amendment to the specification at page 13, line 3 will not be entered because the original grammar was correct. Beginning at line 1 the sentence reads, "... a solid support matrix ... is employed ...".

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-5 and 7-23 stand finally rejected under 35 U.S.C. § 103 as being unpatentable over Sasaki et al. (1979) or Sasaki et al. 1981) in view of Kasche et al. (1990), Teichberg (1990) and Jost et al. (1974).

It is argued that the claimed invention is directed to a composition. It is urged that *in re Vaeck* and *ex parte Stauber and Eberle* require that 1) the prior art suggest the claimed composition, 2) the prior art provides a reasonable likelihood of success, 3) there is some logical basis for combining the prior art references - motivation - so as to obtain the claimed invention. It is urged that *in re Deuell* requires consideration of similarity to prior art compositions. Accordingly it is urged that a *prima facie* case has not been established over the instantly amended claimed compositions.

Sasaki et al. is said not to disclose the claimed compositions having a binding pH of 5-9. The disclosed Amberlite resins require a pH of 4.5 or less for binding. It is argued that Sasaki et al.

do not teach any other suitable resin and do not suggest a solution to the problem they themselves posed of having the disadvantage of functioning only at acidic pH values.

It is argued that the secondary references fail to remedy this deficiency. Kasche et al. is said to binds protein at a pH where the resin is charged (7.5) whereas the resin is uncharged above pH 8. It is asserted that Teichberg and Jost et al. are irrelevant because Teichberg is concerned with affinity-repulsion chromatography, and Jost et al. is simply concerned with whether binding is by ionic or hydrophobic interactions to the resin. In both cases it is asserted that binding of protein to the resin occurs when the resin is charged contrary to the instant claimed application.

Sasaki et al. (1982) provide a cartoon explaining the proposed mechanism of hydrophobic-ionic chromatography in Figure 5. The cartoon clearly indicates, in general terms, that with an acidic group binding occurs below a certain pH and desorption occurs above the critical pH. Different proteins having different interacting groups are released at different critical pH values (X or Y). The figure legend clearly states, "in the case of Amberlite CG-50, X is 4.5". The legend goes on to recite "with the use of appropriate adsorbent carrying alkaline groups, ... the relationship to pH would be opposite". Sasaki et al. do admit that a limitation of the Amberlite is that it can only be used at acidic pH values below 4.5. Hence, Sasaki et al. realize the limits of the specific resin that they used. Nevertheless, Sasaki et al. do suggest the general mechanism of the hydrophobic ionic chromatography method and even suggest the use of alternative "appropriate" functional groups on the resin to obtain other pH regimes.

The disclosure in Sasaki et al. (1982) provides ample motivation for a person of ordinary skill in the art to select other "appropriate groups" on the resin when the protein to be purified by

this method is not stable at acidic pH values. A person of ordinary skill in the art would either know of the pH stability of the protein that they want to purify, or they could readily determine the pH stability with nothing more than routine experimentation known to those of ordinary skill in the art.

Further, a person of ordinary skill in the art is aware of and would be able to select appropriate functional groups having ionizable groups which ionize over the pH range where the protein is stable. As evidence of this awareness and the ease with which the useable pH range of a given resin can be determined, Kasche et al., Teichberg, and Jost et al. were cited. The mere fact that protein binds at a pH where some charge is on the resin does not discredit their disclosure of the pH range where the resin ionizes. Kasche et al. recognize that the method can be used even when the resin is partially charged. Rather than teaching away from the claimed invention, this disclosure extends it. In a sense, this is an extension of the cartoon described by Sasaki et al. (1982). In the pH regime between X and Y, the protein represented by the triangle is still bound to the resin. Kasche et al. is a confirmation of the prediction of Sasaki et al. that a protein can still bind to the resin which is partially charged. The differential affinity of proteins for the resin at different extents of resin/protein charge resulting from changes in pH is the basis for further purification as is well known in the art of protein purification which is amply discussed in the technical literature provided by the manufacturers of ion exchange resins.

As a consequence, a person of ordinary skill in the art would have sufficient motivation to select other ion exchange resins having functional groups which ionize in a pH range which will be suitable for the purification of a desired protein. Further a person of ordinary skill in the art would

be able to select an appropriate resin based upon the teachings of the prior art or through routine experimentation. There is more than a reasonable likelihood of success in using resins which ionize at other pH values compared to Sasaki et al. even to the use of pH values where the resin is partially charged as predicted by Sasaki et al. and demonstrated by Kasche et al. The claimed method involves only recognition of the pH stability range of the protein which should be known or readily measured by the person of ordinary skill in the art, and the selection of an appropriate resin which ionizes in the pH range where the protein is stable. Both of these requirements are suggested by the prior art and require nothing more than routine application of the teachings of Sasaki et al.

The arguments filed 24 February 1997 have been fully considered but they are not deemed to be persuasive. The rejection under 35 U.S.C. § 103 is adhered to for the reasons of record at pages 3-7 of the Office action of 19 August 1996 and the additional reasons above.

No claims are allowed.

Any inquiry concerning this communication should be directed to Jon P. Weber, Ph.D. at telephone number (703) 308-4015. The examiner can normally be reached during the hours of 06:30 to 16:30 Eastern (off first Friday).

If attempts to reach the examiner by telephone are unsuccessful, a message may be left on the voice mail. The fax number for Art Unit 1808 is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J.P.W. March 6, 1997

Jon P. Weber, Ph.D.
Primary Examiner, 1808